PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference R 41247	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/06912	International filing date *(day/month/year)* 30.06.2003	Priority date *(day/month/year)* 03.07.2002
International Patent Classification (IPC) or both national classification and IPC C07K16/28		
Applicant IGENEON KREBS-IMMUNTHERAPIE FORSCHUNGS-UND..et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
26.01.2004	23.09.2004
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Le Flao, K Telephone No. +31 70 340-1040

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/06912

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-22 as originally filed

Claims, Numbers

1-23 received on 30.06.2004 with letter of 30.06.2004

Drawings, Figures

1-7 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☒ the claims, Nos.: 24

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 21

   because:

   ☒ the said international application, or the said claims Nos. 21 relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-23
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-23
Industrial applicability (IA)	Yes:	Claims	1-20,22,23
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claim 21 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

For the assessment of the present claim 21 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: EP 0 528 767 A (SANDOZ AG ;SANDOZ LTD (CH); SANDOZ AG (DE)) 24 February 1993 (1993-02-24)

D2: DETTKE M ET AL: "Different types of FCgamma-receptors are involved in anti-Lewis Y antibody induced effector functions in vitro" BRITISH JOURNAL OF CANCER, vol. 82, no. 2, January 2000, pages 441-445, XP001172841 ISSN: 0007-0920

D3: BASU A ET AL: "Presence of tumor-associated antigens in epidermal growth factor receptors from different human carcinomas." CANCER RESEARCH. UNITED STATES 15 MAY 1987, vol. 47, no. 10, 15 May 1987, pages 2531-2536, XP008024280 ISSN: 0008-5472

D4: GOOI H C ET AL: "Monoclonal antibody (EGR/G49) reactive with the epidermal growth factor receptor of A431 cells recognizes the blood group ALeb and ALey structures." MOLECULAR IMMUNOLOGY. ENGLAND JUN 1985, vol. 22, no. 6, June

1985 (1985-06), pages 689-693, XP008024281 ISSN: 0161-5890

D5: BRICH Z ET AL: "PREPARATION AND CHARACTERIZATION OF A WATER SOLUBLE DEXTRAN IMMUNOCONJUGATE OF DOXORUBICIN AND THE MONOCLONAL ANTIBODY (ABL 364)" JOURNAL OF CONTROLLED RELEASE, ELSEVIER SCIENCE PUBLISHERS B.V. AMSTERDAM, NL, vol. 19, no. 1 / 3, 1 March 1992 (1992-03-01), pages 245-257, XP000261548 ISSN: 0168-3659

Document D1 discloses antibodies binding the difucosyl Lewis blood group antigens Y-6 and B-7-2 normally associated with cancer of epithelial origin and chimeric human/mouse and humanized forms of these monoclonal antibodies (p.1, l.1 to l.26). Their use in diagnostic and therapy is also disclosed (p.1, l.5) and their CDC and ADCC activity has been tested (examples 3 and 4).

Document D2 discloses that ABL 364, a monoclonal antibody recognizing the Lewis Y carbohydrate antigen expressed on epithelial tumor cells, is tested in clinical trials and shows clinical benefit especially for patients with minimal residual cancer disease. The advantage of using a fully humanized antibody is put forward (p.441, left-hand column, l.1 to right-hand column, l.17).

Document D3 discloses monoclonal antibodies specific for sialylated Lewis and difucosylated structures of the Y type that bind to EGF receptors expressed by antigen-positive carcinoma but not to EGFR from normal tissues (p.2531, left-hand column).

Document D4 discloses monoclonal antibodies raised against the EGFR of the epidermoid carcinoma cell line A431 that recognize the difucosylated blood group structures ALe b and ALe y. Such antibodies are used to detect antigenic markers of neoplastic cells (p.689, left-hand column to right-hand column).

Document D5 discloses an immunoconjugate of doxorubicin and the monoclonal antibody ABL 364 binding to Y and B-2 glycolipidic antigens. The immunoconjugate retains binding capacity to human breast carcinoma and part of the free doxorubicin cytotoxic activity (p.245, left-hand column to p.246, left-hand column and p.246, right-hand column, l.39 to p.247, left-hand column, l.4).

NOVELTY (Article 33(2) PCT)

The subject-matter of claims 1-23, dealing with the therapeutical use of an antibody directed against a tumor-associated glycosylation is new over the cited prior art.

INVENTIVE STEP (Article 33(3) PCT)

Document D2, which is considered to represent the most relevant state of the art, discloses (cf. above) the therapeutical use to treat cancer of a monoclonal antibody recognizing the Lewis Y carbohydrate antigen expressed on epithelial tumor cells from which the subject-matter of claim 1 differs in that the antibody inhibits glycosylated tumor cell receptors. The effect of the difference is that the antibody binds to glycosylated tumor cell receptors. The problem to be solved by the present invention may therefore be regarded as providing an antibody binding a tumor-associated glycosylation and inhibiting tumor growth.

The solution proposed in claim 1 of the present application cannot be considered as involving an inventive step (Article 33(3) PCT) for the following reasons. Document D3 discloses monoclonal antibodies specific for sialylated Lewis and difucosylated structures of the Y type that bind to EGF receptors expressed by antigen-positive carcinoma but not to EGFR from normal tissues (p.2531, left-hand column). It is therefore considered as obvious for a skilled person, namely a specialist of cell biology working in the field of cancerology and trying to solve the problem posed to combine D3 with D2 and to test whether the antibody binding to a tumor-associated glycosylation also binds and inhibits glycosylated tumor cell receptors.

Further characterising an antibody binding to a tumor-associated glycosylation by its capacity to bind to and to inhibit glycosylated tumor cell receptors does not involve any inventive step since this further characterisation of a known antibody can be predicted as shown in document D3. Therefore it is considered that the subject-matter of claim 1 does not involve an inventive step (Article 33(3) PCT).

The dependent claims do not appear to contain any additional features which, in combination with the features of claim 1, involve an inventive step as the relevant subject matter is either disclosed in the cited prior art of falls within the knowledge and ability of the skilled person.

OTHER REMARKS

Since independent claims 14, 15, 19 & 21-23 do not contain technical features characterising the antibody itself, the subject-matter of these claims does not meet the requirement following from Article 6 PCT taken in combination with Rule 6.3(b) PCT that any independent claim must contain all the technical features essential to the definition of the invention.